STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 99426

TO: Samuel W Liu **Location: 9d08 / 9b01** **Tuesday, July 22, 2003** **Art Unit: 1653** **Phone: 306-3483** **Serial Number: 09 / 529232**	**From: Jan Delaval** **Location: Biotech-Chem Library** **CM1-1E07** **Phone: 308-4498** **jan.delaval@uspto.gov**

Search Notes

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

Access DB# 95426

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Samuel W Liu Examiner #: 79120 Date: 7-22-03
Art Unit: 1653 Phone Number 306-3483 Serial Number: 09/528,232
Mail Box and Bldg/Room Location: 9D08/9B01 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

_____

Earliest Priority Filing Date: _____

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

please search (1) Formula I of Claim 1 wherein the limitations with repect to Formula I have been described in the claim.

(2) Sequence #24 (SEQ ID NO:3 in Number 24

[NOTE: Both searches are amino acid sequences.].

Thanks!

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

****

STAFF USE ONLY

Searcher: _____
Searcher Phone #: 4498
Searcher Location: _____
Date Searcher Picked Up: 7/21/03

Type of Search

NA Sequence (#) _____
AA Sequence (#) ✓
Structure (#) _____
Bibliographic

Vendors and cost where applicable

STN ✓
Dialog _____
Questel/Orbit _____
Dr Link

→ 1015-1997.


```
=> fil reg
FILE 'REGISTRY' ENTERED AT 18:22:38 ON 22 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   21 JUL 2003  HIGHEST RN 552272-14-7
DICTIONARY FILE UPDATES:  21 JUL 2003  HIGHEST RN 552272-14-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d sqide can tot l21

L21  ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   223120-26-1  REGISTRY
CN   D-Glutamic acid, N2-[[4-(1,1-dimethylethyl)phenyl]sulfonyl]-L-arginyl-(2R)-
     2-piperidinecarbonyl-3-(2-thienyl)-D-alanylglycylglycylglycyl-.beta.-
     alanyl-L-.alpha.-aspartyl-L-tyrosyl-L-.alpha.-glutamyl-L-prolyl-L-
     isoleucyl-L-prolyl-L-.alpha.-glutamyl-L-.alpha.-glutamyl-L-alanyl-3-
     cyclohexyl-L-alanyl- (9CI)  (CA INDEX NAME)
FS   PROTEIN SEQUENCE; STEREOSEARCH
SQL  18
NTE  modified (modifications unspecified)
```

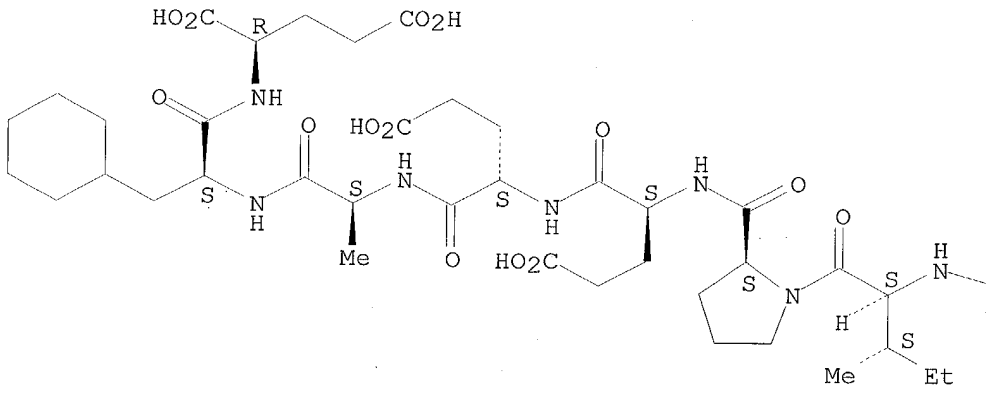
type	------ location ------		description
uncommon	Pip-2	-	-
uncommon	Thi-3	-	-
uncommon	Bal-7	-	-
modification	Arg-1	-	undetermined modification
modification	Ala-17	-	cyclohexyl<Chx>

```
SEQ      1 RXXGGGXDYE PIPEEAAE

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF   C99 H143 N21 O32 S2
SR   CA
LC   STN Files:   CA, CAPLUS

Absolute stereochemistry.
```

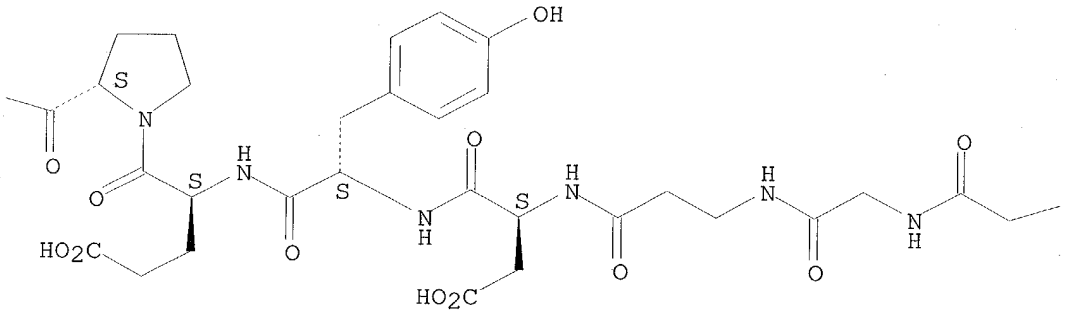
Seq # 24

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1507 - 703-306-4498
jan.delaval@uspto.gov

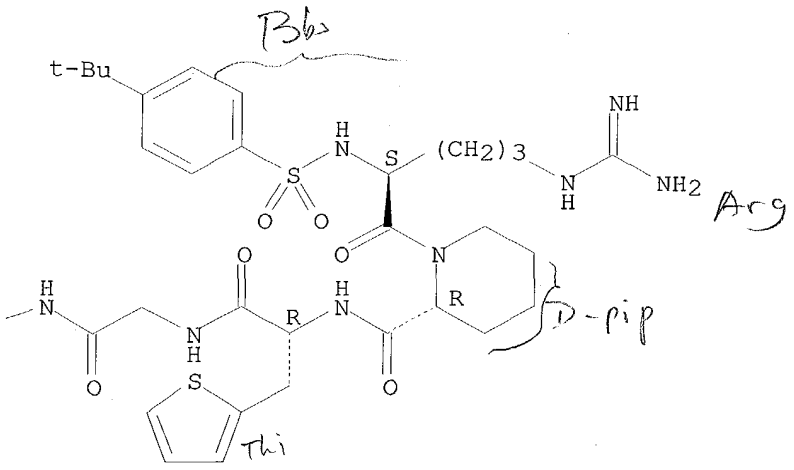
PAGE 1-A



PAGE 1-B



PAGE 1-C



2 REFERENCES IN FILE CA (1947 TO DATE)
2 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 132:262009

REFERENCE 2: 130:297001

L21 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS on STN
RN **223120-12-5** REGISTRY
CN D-Glutamic acid, N2-[[4-(1,1-dimethylethyl)phenyl]sulfonyl]-L-arginyl-(2R)-2-piperidinecarbonyl-3-(2-thienyl)-L-alanylglycylglycylglycyl-.beta.-alanyl-L-.alpha.-aspartyl-L-tyrosyl-L-.alpha.-glutamyl-L-prolyl-L-isoleucyl-L-prolyl-L-.alpha.-glutamyl-L-.alpha.-glutamyl-L-alanyl-3-cyclohexyl-L-alanyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 18
NTE modified (modifications unspecified)

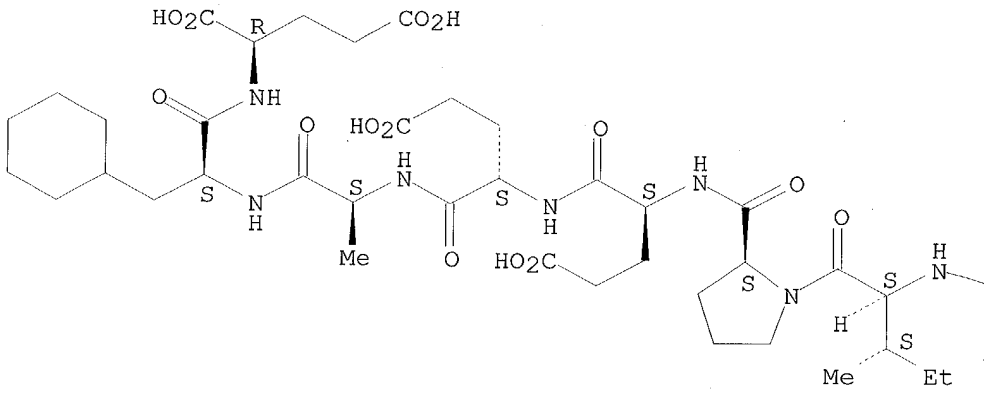
type	------ location ------		description
uncommon	Pip-2	-	-
uncommon	Thi-3	-	-
uncommon	Bal-7	-	-
modification	Arg-1	-	undetermined modification
modification	Ala-17	-	cyclohexyl<Chx>

SEQ 1 RXXGGGXDYE PIPEEAAE

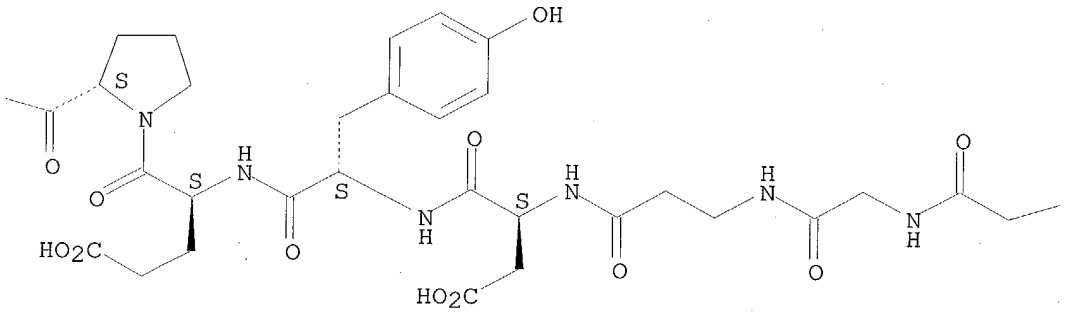
RELATED SEQUENCES AVAILABLE WITH SEQLINK
MF C99 H143 N21 O32 S2
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

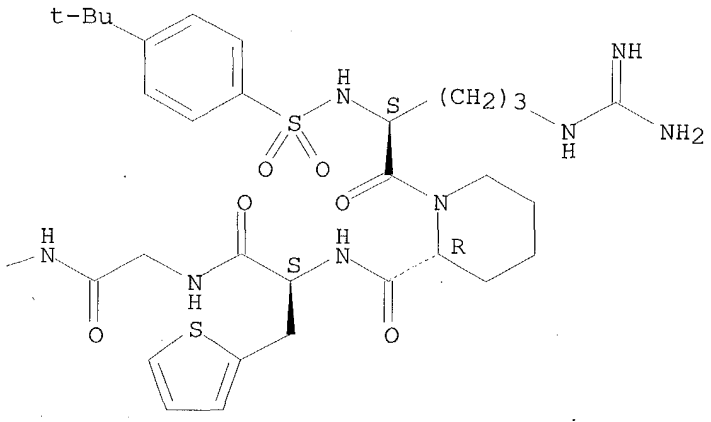
PAGE 1-A



PAGE 1-B



PAGE 1-C



2 REFERENCES IN FILE CA (1947 TO DATE)
2 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 132:262009

REFERENCE 2: 130:297001

=>
=>

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 18:24:32 ON 22 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1907 - 22 Jul 2003 VOL 139 ISS 4
FILE LAST UPDATED: 21 Jul 2003 (20030721/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all tot

L30 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:94674 HCAPLUS

DN 132:262009
TI Design of P1' and P3' Residues of Trivalent **Thrombin** Inhibitors and Their Crystal Structures
AU **Slon-Usakiewicz, Jacek J.**; Sivaraman, J.; Li, Yunge; Cygler, Miroslaw; **Konishi, Yasuo**
CS Biotechnology Research Institute, National Research Council of Canada, Montreal, QC, H4P 2R2, Can.
SO Biochemistry (2000), 39(9), 2384-2391
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 7-3 (Enzymes)
Section cross-reference(s): 75
AB Synthetic bivalent **thrombin** inhibitors comprise an active site blocking segment, a fibrinogen recognition exosite blocking segment, and a linker connecting these segments. Possible nonpolar interactions of the P1' and P3' residues of the linker with **thrombin** S1' and S3' subsites, resp., were identified using the "Methyl Scan" method [Slon-Usakiewicz et al. (1997) Biochem. 36, 13494-13502]. A series of inhibitors (4-tert-butylbenzenesulfonyl)-Arg-(D-pipecolic acid)-Xaa-Gly-Yaa-Gly-.beta.Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-(.beta.-cyclohexylalanine)-(D-Glu)-OH, in which nonpolar P1' residue Xaa or P3' residue Yaa was incorporated, were designed and improved the affinity to **thrombin**. Substitution of the P3' residue with D-phenylglycine or D-Phe improved the Ki value to (9.5 .+-. 0.6) .times. 10-14 or 1.3 .+-. 0.5 .times. 10-13 M, resp., compared to that of a ref. inhibitor with Gly residues at Xaa and Yaa residues (Ki = (2.4 .+-. 0.5) .times. 10-11 M). Similarly, substitution of the P1' residue with L-norleucine or L-.beta.-(2-thienyl)alanine lowered the Ki values to (8.2 .+-. 0.6) .times. 10-14 or (5.1 .+-. 0.4) .times. 10-14 M, resp. The linker Gly-Gly-Gly-.beta.Ala of the inhibitors in the previous sentence was simplified with 12-aminododecanoic acid, resulting in further improvement of the Ki values to (3.8 .+-. 0.6) .times. 10-14 or (1.7 .+-. 0.4) .times. 10-14 M, resp. These Ki values are equiv. to that of natural hirudin (2.2 .times. 10-14 M), yet the size of the synthetic inhibitors (2 kD) is only one-third that of hirudin (7 kD). Two inhibitors, with L-norleucine or L-.beta.-(2-thienyl)alanine at the P1' residue and the improved linker of 12-aminododecanoic acid, were crystd. in complex with human .alpha.-**thrombin**. The crystal structures of these complexes were solved and refined to 2.1 .ANG. resoln. The Lys60F side chain of **thrombin** moved significantly and formed a large nonpolar S1' subsite to accommodate the bulky P1' residue.
ST trivalent **thrombin** inhibitor design crystal structure
IT Enzyme functional sites
(active; design of P1' and P3' residues of trivalent **thrombin** inhibitors and their crystal structures)
IT Enzyme kinetics
(of inhibition; design of P1' and P3' residues of trivalent **thrombin** inhibitors and their crystal structures)
IT Crystal structure
(of trivalent **thrombin** inhibitors complexed with **thrombin**)
IT Structure-activity relationship
(**thrombin**-inhibiting; design of P1' and P3' residues of trivalent **thrombin** inhibitors and their crystal structures)
IT **9002-04-4D, Thrombin**, complexes with trivalent **thrombin** inhibitors 263367-63-1D, complexes with **thrombin** 263367-64-2D, complexes with **thrombin**
RL: PRP (Properties)
(crystal structure; design of P1' and P3' residues of trivalent **thrombin** inhibitors and their crystal structures)
IT 197518-05-1 197518-06-2 197518-07-3 197518-08-4 197519-06-5

223117-53-1 223117-64-4 223117-70-2 223117-75-7 223117-81-5
223117-89-3 223117-95-1 223118-14-7 223118-20-5 223118-31-8
223118-41-0 223118-52-3 223118-59-0 223118-64-7 223118-70-5
223118-76-1 223118-82-9 223118-88-5 223119-00-4 223119-13-9
223119-22-0 223119-28-6 223119-36-6 223119-45-7 223119-53-7
223119-62-8 223119-72-0 223119-78-6 223119-87-7 223119-93-5
223120-02-3 **223120-12-5** **223120-26-1** 223120-49-8
223120-63-6 223120-68-1 223120-74-9 223120-84-1 223120-90-9
223120-97-6 223121-11-7 223121-17-3 223121-22-0 223121-31-1
223121-36-6 223121-41-3 223121-48-0 223121-54-8 223121-58-2
223121-63-9 223121-68-4 223121-74-2 223121-88-8 223121-94-6
223122-01-8 223122-06-3 223122-18-7 223122-23-4 223122-27-8
223122-31-4 223122-37-0 223122-44-9 223122-52-9 223122-63-2
223122-72-3 223122-83-6 263367-65-3 263367-66-4 263367-67-5
263367-68-6 263367-69-7 263367-70-0 263367-74-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(design of P1' and P3' residues of trivalent **thrombin** inhibitors and their crystal structures)

IT **9002-04-4, Thrombin**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(design of P1' and P3' residues of trivalent **thrombin** inhibitors and their crystal structures)

RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Blomback, B; Nature 1967, V215, P1445 HCAPLUS
(2) Bode, W; EMBO J 1989, V8, P3467 HCAPLUS
(3) Bourdon, P; FEBS Lett 1991, V294, P163 HCAPLUS
(4) Brunger, A; X-plor version 3.1 1993
(5) Charles, R; J Med Chem 1999, V42, P1376
(6) Dimaio, J; FEBS Lett 1991, V282, P47 HCAPLUS
(7) Dimaio, J; J Biol Chem 1990, V265, P21698 HCAPLUS
(8) Dimaio, J; J Med Chem 1992, V35, P3331 HCAPLUS
(9) Fethiere, J; Protein Sci 1996, V5, P1174 HCAPLUS
(10) Jones, T; Acta Crstallogr 1991, VA47, P110 HCAPLUS
(11) Kline, T; Biochem Biophys Res Commun 1991, V177, P1049 HCAPLUS
(12) Krishnan, R; Protein Sci 1996, V5, P422 HCAPLUS
(13) Laudano, A; Ann N Y Acad Sci 1983, V27, P315
(14) Le Bonniec, B; Biochemistry 1996, V35, P7114 HCAPLUS
(15) Lombardi, A; J Med Chem 1996, V39, P2008 HCAPLUS
(16) Lombardi, A; Protein Sci 1999, V8, P91 HCAPLUS
(17) Maraganore, J; Biochemistry 1990, V29, P7095 HCAPLUS
(18) Martin, P; J Biol Chem 1992, V267, P7911 HCAPLUS
(19) Matthews, J; Biophys J 1996, V71, P2830 HCAPLUS
(20) Minor, W; XDISPLAY 1993
(21) Okuyama, K; Biopolymers 1996, V40, P85 HCAPLUS
(22) Otwinowski, Z; Proceedings of the CCP4 Study Weekend:Data Collection and Processing 1993, P56
(23) Qiu, X; Biochemistry 1992, V31, P11689 HCAPLUS
(24) Rehse, P; Biochemistry 1995, V34, P11537 HCAPLUS
(25) Rezaie, A; Biochemistry 1997, V36, P1026 HCAPLUS
(26) Schechter, I; Biochem Biophys Res Commun 1967, V27, P157 HCAPLUS
(27) Segel, I; Enzyme Kinetics:Behawior and Analysis of Rapid Equilibrium and Steady-State Enzyme Systems 1975, P100
(28) Skordalakes, E; Biochemistry 1998, V37, P14420 HCAPLUS
(29) Skrzypczak-Jankun, E; J Mol Biol 1991, V221, P1379 HCAPLUS
(30) Slon-Usakiewicz, J; Biochemistry 1997, V36, P13494 HCAPLUS
(31) Stephens, A; J Biol Chem 1988, V263, P3639
(32) Stubbs, M; Thrombin Res 1993, V69, P1 HCAPLUS
(33) Szewczuk, Z; Biochemistry 1992, V31, P9132 HCAPLUS
(34) Szewczuk, Z; Biochemistry 1993, V32, P3396 HCAPLUS
(35) Theunissen, H; J Biol Chem 1993, V268, P9035 HCAPLUS

(36) Tsuda, Y; Biochemistry 1994, V33, P14443 HCAPLUS
(37) Vu, T; Cell 1991, V64, P1057 HCAPLUS
(38) Wnendt, S; Protein Eng 1997, V10, P169 HCAPLUS
(39) Zdanov, A; Proteins 1993, V17, P252 HCAPLUS

L30 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:271384 HCAPLUS
DN 130:297001
TI Preparation of trivalent **thrombin** inhibitors
IN **Konishi, Yasuo; Slon, Jacek**
PA National Research Council of Canada, Can.
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07K014-815
ICS A61K038-58
CC 34-3 (**Amino Acids, Peptides**, and **Proteins**)
Section cross-reference(s): 1, 7
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI WO 9919356	A1	19990422	WO 1997-CA745	19971015	<--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
AU 9746122	A1	19990503	AU 1997-46122	19971015	<--
AU 761011	B2	20030529			
EP 1023324	A1	20000802	EP 1997-944656	19971015	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
NZ 503669	A	20010928	NZ 1997-503669	19971015	<--
JP 2001519442	T2	20011023	JP 2000-515927	19971015	<--
PRAI WO 1997-CA745	A	19971015	<--		

OS MARPAT 130:297001
AB Trivalent **thrombin** inhibitors AS-Z-P (AS represents an S subsite blocking segment, P represents a fibrinogen recognition exosite blocking segment, Z represents a S' subsite blocking segment) or their pharmaceutically acceptable salts, were prepd. The S' subsite blocking segment, besides binding to the **thrombin** S' subsites, connects the S subsite blocking segment and the fibrinogen recognition exosite blocking segment. This binding of Z segment together with the bindings of the AS and P segments, contributes to improve the affinity of the inhibitors significantly. The AS blocking segment and the P segment preferably have the sequence Bbs-Arg-D-Pip- (Bbs = 4-tert-butylbenzenesulfonyl, Pip = pipecolic acid) and Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH (Cha = .beta.-cyclohexylalanine), resp. The Z segment preferably has the sequence Xaa-Gly-Yaa-Gly-.beta.-Ala where: Xaa, Yaa = Gly, Ala, D-Ala, Val, D-Val, Phe, D-Phe, His, D-His, Nva, D-Nva, Ile, D-Ile, Nle, D-Nle, .alpha.Aib (2-aminoisobutyric acid), Phg (phenylglycine), D-Phg, Thi (.beta.-(2-thienyl)alanine), D-Thi, Chg (cyclohexylglycine), etc. Thus, Bbs-Arg-D-Pip-Thi-Gly-Gly-Gly-.beta.-Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH, having a Ki value of 0.051 .+-. 0.004 pM, was prepd. by the solid phase method using a conventional Fmoc procedure. The preferred inhibitors have Ki values smaller the 1 pM and are useful for treating or preventing vascular diseases.

ST peptide prepn trivalent **thrombin** inhibitor
IT **Peptides**, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of trivalent **thrombin** inhibitors)
IT Blood vessel, disease
(treatment of; prepn. of trivalent **thrombin** inhibitors)
IT **9002-04-4, Thrombin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; prepn. of trivalent **thrombin** inhibitors)
IT 197518-05-1P 197518-06-2P 197518-07-3P 197518-08-4P 197519-06-5P
223117-53-1P 223117-64-4P 223117-70-2P 223117-75-7P 223117-81-5P
223117-89-3P 223117-95-1P 223118-04-5P 223118-14-7P 223118-20-5P
223118-31-8P 223118-41-0P 223118-52-3P 223118-59-0P 223118-64-7P
223118-70-5P 223118-76-1P 223118-82-9P 223118-88-5P 223119-00-4P
223119-07-1P 223119-13-9P 223119-22-0P 223119-28-6P 223119-36-6P
223119-45-7P 223119-53-7P 223119-62-8P 223119-72-0P 223119-78-6P
223119-87-7P 223119-93-5P 223120-02-3P **223120-12-5P**
223120-26-1P 223120-49-8P 223120-63-6P 223120-68-1P
223120-74-9P 223120-84-1P 223120-90-9P 223120-97-6P 223121-04-8P
223121-11-7P 223121-17-3P 223121-22-0P 223121-31-1P 223121-36-6P
223121-41-3P 223121-48-0P 223121-54-8P 223121-58-2P 223121-63-9P
223121-68-4P 223121-74-2P 223121-81-1P 223121-88-8P 223121-94-6P
223122-01-8P 223122-06-3P 223122-18-7P 223122-23-4P 223122-27-8P
223122-31-4P 223122-37-0P 223122-44-9P 223122-52-9P 223122-63-2P
223122-72-3P 223122-83-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of trivalent **thrombin** inhibitors)
IT **9002-04-4, Thrombin**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.alpha.-; prepn. of trivalent **thrombin** inhibitors)
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Konishi, Y; WO 9511921 A 1995 HCAPLUS
(2) Krishnan; PROTEIN SCIENCE 1996, V5(3), P422 HCAPLUS
(3) Szewczuk, E; BIOCHEMISTRY 1993, V32(13), P3396
(4) Tsuda, E; BIOCHEMISTRY 1994, V33(48), P14443

=> fil reg
FILE 'REGISTRY' ENTERED AT 18:32:11 ON 22 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 21 JUL 2003 HIGHEST RN 552272-14-7
DICTIONARY FILE UPDATES: 21 JUL 2003 HIGHEST RN 552272-14-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP

```
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d sta que l31
L31         132 SEA FILE=REGISTRY ABB=ON  PLU=ON  .G.G'BAL'/SQSP


=> d his

     (FILE 'HOME' ENTERED AT 18:06:50 ON 22 JUL 2003)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 18:07:01 ON 22 JUL 2003
               E WO97-CA745/AP,PRN
L1           1 S E3,E4
               E KONISHI Y/AU
L2         275 S E3,E5,E14
               E SLON J/AU
L3          18 S E3-E7
L4         292 S L2,L3

     FILE 'REGISTRY' ENTERED AT 18:08:01 ON 22 JUL 2003
L5           1 S 9002-04-4

     FILE 'HCAPLUS' ENTERED AT 18:08:59 ON 22 JUL 2003
L6       15808 S L5
L7       30027 S THROMBIN
L8         495 S THROMBASE OR THROMBOFORT OR THROMBOSTAT OR TROPOSTASIN# OR FA
L9          69 S BLOOD COAGULATION FACTOR IIA
L10        116 S BLOOD COAGULATION FACTOR II(L)ACTIVAT?
L11      30683 S L6-L10
L12         39 S L4 AND L11
L13          9 S L12 AND (PEPTIDE# OR PROTEIN# OR AMINO ACID#)/SC,SX
L14          9 S L12 AND (PEPTIDE# OR PROTEIN# OR AMINO(L)ACID#)/CW
L15         13 S L13,L14
L16          1 S L1 AND L15
L17         12 S L15 NOT L16
               SEL RN L16

     FILE 'REGISTRY' ENTERED AT 18:10:51 ON 22 JUL 2003
L18         76 S E1-E76
L19         75 S L18 AND 46.150.18/RID
L20          4 S L19 AND (SC4 AND NC4 AND NC5)/ES AND 46.150.18/RID
               SEL RN 3 4
L21          2 S L20 AND E77-E78
               E C99H143N21O32S2/MF
L22          4 S E3
L23          2 S L22 NOT L21

     FILE 'HCAOLD' ENTERED AT 18:22:02 ON 22 JUL 2003
L24          0 S L21

     FILE 'HCAPLUS' ENTERED AT 18:22:06 ON 22 JUL 2003
L25          2 S L21
L26          2 S L25 AND L1-L4,L6-L17

     FILE 'USPATFULL, USPAT2' ENTERED AT 18:22:22 ON 22 JUL 2003
L27          0 S L21

     FILE 'REGISTRY' ENTERED AT 18:22:38 ON 22 JUL 2003

     FILE 'HCAPLUS' ENTERED AT 18:22:50 ON 22 JUL 2003
```

```
                E SLON USAKIEWICZ/AU
L28           12 S E4-E7
L29            1 S L25,L26 AND L28
L30            2 S L26,L29

     FILE 'HCAPLUS' ENTERED AT 18:24:32 ON 22 JUL 2003

     FILE 'REGISTRY' ENTERED AT 18:25:05 ON 22 JUL 2003
L31          132 S .G.G'BAL'/SQSP
                SAV L31 LIU529/A
L32          130 S L31 NOT L21

     FILE 'HCAPLUS' ENTERED AT 18:26:12 ON 22 JUL 2003
                SET SMARTSELECT ON
L33          SEL L30 1- RN :      85 TERMS
                SET SMARTSELECT OFF

     FILE 'REGISTRY' ENTERED AT 18:26:12 ON 22 JUL 2003
L34           85 S L33
L35           85 S L34,L18
L36           75 S L32 AND L35
L37           55 S L32 NOT L36
L38            6 S L37 AND 46.150.1/RID
L39           11 S L37 AND NC4/ES
L40            5 S L39 NOT L38
L41            6 S L37 AND NC5/ES
L42            6 S L41,L38
L43           81 S L36,L42
                SAV L43 LIU529A/A

     FILE 'HCAOLD' ENTERED AT 18:3
L44            0 S L43

     FILE 'USPATFULL, USPAT2' ENTE                          L 2003
L45            0 S L43

     FILE 'HCAPLUS' ENTERED AT 18:31:15 ON 22 JUL 2003
L46            3 S L43
L47            3 S L46 AND L1-L4,L6-L17,L28
L48            3 S L31 AND L47

     FILE 'REGISTRY' ENTERED AT 18:32:11 ON 22 JUL 2003

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 18:32:25 ON 22 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
```

81 seq hits ←

3 references ↙

FILE COVERS 1907 - 22 Jul 2003 VOL 139 ISS 4
FILE LAST UPDATED: 21 Jul 2003 (20030721/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l48 all tot

L48 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:94674 HCAPLUS
DN 132:262009
TI Design of P1' and P3' Residues of Trivalent **Thrombin** Inhibitors and Their Crystal Structures
AU **Slon-Usakiewicz, Jacek J.**; Sivaraman, J.; Li, Yunge; Cygler, Miroslaw; **Konishi, Yasuo**
CS Biotechnology Research Institute, National Research Council of Canada, Montreal, QC, H4P 2R2, Can.
SO Biochemistry (2000), 39(9), 2384-2391
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 7-3 (Enzymes)
Section cross-reference(s): 75
AB Synthetic bivalent **thrombin** inhibitors comprise an active site blocking segment, a fibrinogen recognition exosite blocking segment, and a linker connecting these segments. Possible nonpolar interactions of the P1' and P3' residues of the linker with **thrombin** S1' and S3' subsites, resp., were identified using the "Methyl Scan" method [Slon-Usakiewicz et al. (1997) Biochem. 36, 13494-13502]. A series of inhibitors (4-tert-butylbenzenesulfonyl)-Arg-(D-pipecolic acid)-Xaa-Gly-Yaa-Gly-.beta.Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-(.beta.-cyclohexylalanine)-(D-Glu)-OH, in which nonpolar P1' residue Xaa or P3' residue Yaa was incorporated, were designed and improved the affinity to **thrombin**. Substitution of the P3' residue with D-phenylglycine or D-Phe improved the Ki value to (9.5 .+-. 0.6) .times. 10-14 or 1.3 .+-. 0.5 .times. 10-13 M, resp., compared to that of a ref. inhibitor with Gly residues at Xaa and Yaa residues (Ki = (2.4 .+-. 0.5) .times. 10-11 M). Similarly, substitution of the P1' residue with L-norleucine or L-.beta.-(2-thienyl)alanine lowered the Ki values to (8.2 .+-. 0.6) .times. 10-14 or (5.1 .+-. 0.4) .times. 10-14 M, resp. The linker Gly-Gly-Gly-.beta.Ala of the inhibitors in the previous sentence was simplified with 12-aminododecanoic acid, resulting in further improvement of the Ki values to (3.8 .+-. 0.6) .times. 10-14 or (1.7 .+-. 0.4) .times. 10-14 M, resp. These Ki values are equiv. to that of natural hirudin (2.2 .times. 10-14 M), yet the size of the synthetic inhibitors (2 kD) is only one-third that of hirudin (7 kD). Two inhibitors, with L-norleucine or L-.beta.-(2-thienyl)alanine at the P1' residue and the improved linker of 12-aminododecanoic acid, were crystd. in complex with human .alpha.-**thrombin**. The crystal structures of these complexes were solved and refined to 2.1 .ANG. resoln. The Lys60F side chain of **thrombin** moved significantly and formed a large nonpolar S1' subsite to accommodate the bulky P1' residue.
ST trivalent **thrombin** inhibitor design crystal structure
IT Enzyme functional sites
(active; design of P1' and P3' residues of trivalent **thrombin** inhibitors and their crystal structures)
IT Enzyme kinetics
(of inhibition; design of P1' and P3' residues of trivalent **thrombin** inhibitors and their crystal structures)
IT Crystal structure
(of trivalent **thrombin** inhibitors complexed with **thrombin**)
IT Structure-activity relationship
(**thrombin**-inhibiting; design of P1' and P3' residues of

trivalent **thrombin** inhibitors and their crystal structures)

IT **9002-04-4D, Thrombin,** complexes with trivalent **thrombin** inhibitors 263367-63-1D, complexes with **thrombin** 263367-64-2D, complexes with **thrombin**
RL: PRP (Properties)
(crystal structure; design of P1' and P3' residues of trivalent **thrombin** inhibitors and their crystal structures)

IT **197518-05-1 197518-06-2 197518-07-3**
197518-08-4 197519-06-5 223117-53-1
223117-64-4 223117-70-2 223117-75-7
223117-81-5 223117-89-3 223117-95-1
223118-14-7 223118-20-5 223118-31-8
223118-41-0 223118-52-3 223118-59-0
223118-64-7 223118-70-5 223118-76-1
223118-82-9 223118-88-5 223119-00-4
223119-13-9 223119-22-0 223119-28-6
223119-36-6 223119-45-7 223119-53-7
223119-62-8 223119-72-0 223119-78-6
223119-87-7 223119-93-5 223120-02-3
223120-12-5 223120-26-1 223120-49-8
223120-63-6 223120-68-1 223120-74-9
223120-84-1 223120-90-9 223120-97-6
223121-11-7 223121-17-3 223121-22-0
223121-31-1 223121-36-6 223121-41-3
223121-48-0 223121-54-8 223121-58-2
223121-63-9 223121-68-4 223121-74-2
223121-88-8 223121-94-6 223122-01-8
223122-06-3 223122-18-7 223122-23-4
223122-27-8 223122-31-4 223122-37-0
223122-44-9 223122-52-9 223122-63-2
223122-72-3 223122-83-6 263367-65-3
263367-66-4 263367-67-5 263367-68-6 263367-69-7 263367-70-0
263367-74-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(design of P1' and P3' residues of trivalent **thrombin** inhibitors and their crystal structures)

IT **9002-04-4, Thrombin**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(design of P1' and P3' residues of trivalent **thrombin** inhibitors and their crystal structures)

RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Blomback, B; Nature 1967, V215, P1445 HCAPLUS
(2) Bode, W; EMBO J 1989, V8, P3467 HCAPLUS
(3) Bourdon, P; FEBS Lett 1991, V294, P163 HCAPLUS
(4) Brunger, A; X-plor version 3.1 1993
(5) Charles, R; J Med Chem 1999, V42, P1376
(6) Dimaio, J; FEBS Lett 1991, V282, P47 HCAPLUS
(7) Dimaio, J; J Biol Chem 1990, V265, P21698 HCAPLUS
(8) Dimaio, J; J Med Chem 1992, V35, P3331 HCAPLUS
(9) Fethiere, J; Protein Sci 1996, V5, P1174 HCAPLUS
(10) Jones, T; Acta Crstallogr 1991, VA47, P110 HCAPLUS
(11) Kline, T; Biochem Biophys Res Commun 1991, V177, P1049 HCAPLUS
(12) Krishnan, R; Protein Sci 1996, V5, P422 HCAPLUS
(13) Laudano, A; Ann N Y Acad Sci 1983, V27, P315
(14) Le Bonniec, B; Biochemistry 1996, V35, P7114 HCAPLUS
(15) Lombardi, A; J Med Chem 1996, V39, P2008 HCAPLUS
(16) Lombardi, A; Protein Sci 1999, V8, P91 HCAPLUS
(17) Maraganore, J; Biochemistry 1990, V29, P7095 HCAPLUS
(18) Martin, P; J Biol Chem 1992, V267, P7911 HCAPLUS
(19) Matthews, J; Biophys J 1996, V71, P2830 HCAPLUS

(20) Minor, W; XDISPLAY 1993
(21) Okuyama, K; Biopolymers 1996, V40, P85 HCAPLUS
(22) Otwinowski, Z; Proceedings of the CCP4 Study Weekend:Data Collection and Processing 1993, P56
(23) Qiu, X; Biochemistry 1992, V31, P11689 HCAPLUS
(24) Rehse, P; Biochemistry 1995, V34, P11537 HCAPLUS
(25) Rezaie, A; Biochemistry 1997, V36, P1026 HCAPLUS
(26) Schechter, I; Biochem Biophys Res Commun 1967, V27, P157 HCAPLUS
(27) Segel, I; Enzyme Kinetics:Behavior and Analysis of Rapid Equilibrium and Steady-State Enzyme Systems 1975, P100
(28) Skordalakes, E; Biochemistry 1998, V37, P14420 HCAPLUS
(29) Skrzypczak-Jankun, E; J Mol Biol 1991, V221, P1379 HCAPLUS
(30) Slon-Usakiewicz, J; Biochemistry 1997, V36, P13494 HCAPLUS
(31) Stephens, A; J Biol Chem 1988, V263, P3639
(32) Stubbs, M; Thrombin Res 1993, V69, P1 HCAPLUS
(33) Szewczuk, Z; Biochemistry 1992, V31, P9132 HCAPLUS
(34) Szewczuk, Z; Biochemistry 1993, V32, P3396 HCAPLUS
(35) Theunissen, H; J Biol Chem 1993, V268, P9035 HCAPLUS
(36) Tsuda, Y; Biochemistry 1994, V33, P14443 HCAPLUS
(37) Vu, T; Cell 1991, V64, P1057 HCAPLUS
(38) Wnendt, S; Protein Eng 1997, V10, P169 HCAPLUS
(39) Zdanov, A; Proteins 1993, V17, P252 HCAPLUS

L48 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:271384 HCAPLUS
DN 130:297001
TI Preparation of trivalent **thrombin** inhibitors
IN **Konishi, Yasuo; Slon, Jacek**
PA National Research Council of Canada, Can.
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07K014-815
ICS A61K038-58
CC 34-3 (**Amino Acids, Peptides**, and **Proteins**)
Section cross-reference(s): 1, 7
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9919356	A1	19990422	WO 1997-CA745	19971015	<--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
	AU 9746122	A1	19990503	AU 1997-46122	19971015	<--
	AU 761011	B2	20030529			
	EP 1023324	A1	20000802	EP 1997-944656	19971015	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
	NZ 503669	A	20010928	NZ 1997-503669	19971015	<--
	JP 2001519442	T2	20011023	JP 2000-515927	19971015	<--
PRAI	WO 1997-CA745	A	19971015	<--		

OS MARPAT 130:297001
AB Trivalent **thrombin** inhibitors AS-Z-P (AS represents an S subsite blocking segment, P represents a fibrinogen recognition exosite blocking segment, Z represents a S' subsite blocking segment) or their pharmaceutically acceptable salts, were prepd. The S' subsite blocking

segment, besides binding to the **thrombin** S' subsites, connects the S subsite blocking segment and the fibrinogen recognition exosite blocking segment. This binding of Z segment together with the bindings of the AS and P segments, contributes to improve the affinity of the inhibitors significantly. The AS blocking segment and the P segment preferably have the sequence Bbs-Arg-D-Pip- (Bbs = 4-tert-butylbenzenesulfonyl, Pip = pipecolic acid) and Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH (Cha = .beta.-cyclohexylalanine), resp. The Z segment preferably has the sequence Xaa-Gly-Yaa-Gly-.beta.-Ala where: Xaa, Yaa = Gly, Ala, D-Ala, Val, D-Val, Phe, D-Phe, His, D-His, Nva, D-Nva, Ile, D-Ile, Nle, D-Nle, .alpha.Aib (2-aminoisobutyric acid), Phg (phenylglycine), D-Phg, Thi (.beta.-(2-thienyl)alanine), D-Thi, Chg (cyclohexylglycine), etc. Thus, Bbs-Arg-D-Pip-Thi-Gly-Gly-Gly-.beta.-Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH, having a Ki value of 0.051 .+-. 0.004 pM, was prepd. by the solid phase method using a conventional Fmoc procedure. The preferred inhibitors have Ki values smaller the 1 pM and are useful for treating or preventing vascular diseases.

ST peptide prepn trivalent **thrombin** inhibitor

IT **Peptides**, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of trivalent **thrombin** inhibitors)

IT Blood vessel, disease
(treatment of; prepn. of trivalent **thrombin** inhibitors)

IT **9002-04-4, Thrombin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; prepn. of trivalent **thrombin** inhibitors)

IT **197518-05-1P 197518-06-2P 197518-07-3P**
197518-08-4P 197519-06-5P 223117-53-1P
223117-64-4P 223117-70-2P 223117-75-7P
223117-81-5P 223117-89-3P 223117-95-1P
223118-04-5P 223118-14-7P 223118-20-5P
223118-31-8P 223118-41-0P 223118-52-3P
223118-59-0P 223118-64-7P 223118-70-5P
223118-76-1P 223118-82-9P 223118-88-5P
223119-00-4P 223119-07-1P 223119-13-9P
223119-22-0P 223119-28-6P 223119-36-6P
223119-45-7P 223119-53-7P 223119-62-8P
223119-72-0P 223119-78-6P 223119-87-7P
223119-93-5P 223120-02-3P 223120-12-5P
223120-26-1P 223120-49-8P 223120-63-6P
223120-68-1P 223120-74-9P 223120-84-1P
223120-90-9P 223120-97-6P 223121-04-8P
223121-11-7P 223121-17-3P 223121-22-0P
223121-31-1P 223121-36-6P 223121-41-3P
223121-48-0P 223121-54-8P 223121-58-2P
223121-63-9P 223121-68-4P 223121-74-2P
223121-81-1P 223121-88-8P 223121-94-6P
223122-01-8P 223122-06-3P 223122-18-7P
223122-23-4P 223122-27-8P 223122-31-4P
223122-37-0P 223122-44-9P 223122-52-9P
223122-63-2P 223122-72-3P 223122-83-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of trivalent **thrombin** inhibitors)

IT **9002-04-4, Thrombin**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.alpha.-; prepn. of trivalent **thrombin** inhibitors)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE
(1) Konishi, Y; WO 9511921 A 1995 HCAPLUS
(2) Krishnan; PROTEIN SCIENCE 1996, V5(3), P422 HCAPLUS
(3) Szewczuk, E; BIOCHEMISTRY 1993, V32(13), P3396
(4) Tsuda, E; BIOCHEMISTRY 1994, V33(48), P14443

L48 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:660911 HCAPLUS
DN 127:316126
TI Nonpolar interactions of **thrombin** S' subsites with its bivalent inhibitor: methyl scan of the inhibitor linker
AU **Slon-Usakiewicz, Jacek J.**; Purisima, Enrico; Tsuda, Yuko; Sulea, Traian; Pedyczak, Artur; Fethiere, James; Cygler, Miroslaw; **Konishi, Yasuo**
CS National Research Council of Canada, Biotechnology Research Institute, Montreal, QC, H4P 2R2, Can.
SO Biochemistry (1997), 36(44), 13494-13502
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 7-3 (Enzymes)
AB We have designed bivalent **thrombin** inhibitors, consisting of a nonsubstrate type active site blocking segment, a hirudin-based fibrinogen recognition exosite blocking segment, and a linker connecting these segments. The inhibition provided by the bivalent inhibitors with various linker lengths revealed that a min. of 15 atoms was required for simultaneous binding of the two blocking segments of the inhibitor to **thrombin** without significant distortion. The crystal structure of the inhibitors with a 16-atom linker showed some conformational flexibility in the linker portion which still lies deep in the groove joining the active site and the fibrinogen recognition exosite. Since the **thrombin** S' subsites are not well characterized, we designed a new strategy to search for possible nonpolar interactions between the linker and the **thrombin** S' subsites. This strategy, the "methyl scan", is based on the incorporation of a Me side chain at each atom position of the linker by using sarcosine, D,L-alanine, D,L-3-aminoisobutyric acid, or N-methyl-.beta.-alanine. The Me groups on the second and the eighth atom positions of the linker, which correspond to the side chains of the P1' and the P3' residues, resp., improved the affinity of the inhibitors significantly. Further study of the stereospecificity showed that L-Ala at the P1' residue and D-Ala at the P3' residue preferably improved the affinity of the inhibitors 20- and 25-fold, resp. Mol. modeling calcns. using a Me probe were also carried out to identify favorable nonpolar interacting sites on the **thrombin** surface. Two sites were identified in the vicinity of the P1' and the P3' residues, supporting the validity of the Me scan method. Thus, this study has improved our understanding of the interactions taking place in this groove. In particular, we have been able to show that some specific structural features, such as hydrophobic complementarity between the linker and the **thrombin** S' subsites, could be exploited and make these inhibitors trivalent.
ST **thrombin** inhibitor peptide bivalent interaction
IT Methyl group
(Me scan method; nonpolar interactions of **thrombin** S' subsites with its bivalent inhibitor: Me scan of inhibitor linker)
IT Enzyme functional sites
Molecular association
(nonpolar interactions of **thrombin** S' subsites with its bivalent inhibitor: Me scan of inhibitor linker)
IT Enzyme kinetics
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(of inhibition; nonpolar interactions of **thrombin** S' subsites with its bivalent inhibitor: Me scan of inhibitor linker)

IT Crystal structure
(of **thrombin**-substrate; nonpolar interactions of **thrombin** S' subsites with its bivalent inhibitor: Me scan of inhibitor linker)

IT Conformation
(protein, of **thrombin**-substrate; nonpolar interactions of **thrombin** S' subsites with its bivalent inhibitor: Me scan of inhibitor linker)

IT **Peptides**, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**thrombin** inhibitor; nonpolar interactions of **thrombin** S' subsites with its bivalent inhibitor: Me scan of inhibitor linker)

IT 159218-12-9 159218-18-5 170429-33-1 170429-34-2 170429-35-3
170429-36-4 170429-37-5 170429-38-6 170429-39-7 170429-40-0
170429-43-3 197518-01-7 197518-02-8 197518-03-9 **197518-04-0**
197518-05-1
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(as **thrombin** inhibitor; nonpolar interactions of **thrombin** S' subsites with its bivalent inhibitor: Me scan of inhibitor linker)

IT **197518-06-2 197518-07-3 197518-08-4**
197518-09-5 197518-10-8 **197518-11-9 197518-12-0**
197518-13-1 197518-14-2 197518-15-3 197518-16-4 **197518-17-5**
197518-19-7 197518-21-1 197518-23-3 197518-24-4
197518-26-6 **197518-27-7** 197518-28-8 197518-29-9
197518-31-3 197518-32-4 197518-33-5 197518-34-6 197518-36-8
197518-38-0 197518-39-1 197518-40-4 **197519-06-5**
197717-04-7 197717-09-2 197717-13-8 197717-14-9 197717-16-1
197717-17-2
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(as **thrombin** inhibitor; nonpolar interactions of **thrombin** S' subsites with its bivalent inhibitor: Me scan of inhibitor linker)

IT 107-97-1, Sarcosine 144-90-1, 3-Aminoisobutyric acid 302-72-7, dl-Alanine 2679-14-3, N-Methyl-.beta.-alanine.
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(in Me scan method; nonpolar interactions of **thrombin** S' subsites with its bivalent inhibitor: Me scan of inhibitor linker)

IT **9002-04-4, Thrombin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; nonpolar interactions of **thrombin** S' subsites with its bivalent inhibitor: Me scan of inhibitor linker)

IT **9002-04-4, Thrombin**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nonpolar interactions of **thrombin** S' subsites with its bivalent inhibitor: Me scan of inhibitor linker)

IT 56-41-7, Alanine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(of **thrombin**; nonpolar interactions of **thrombin** S' subsites with its bivalent inhibitor: Me scan of inhibitor linker)

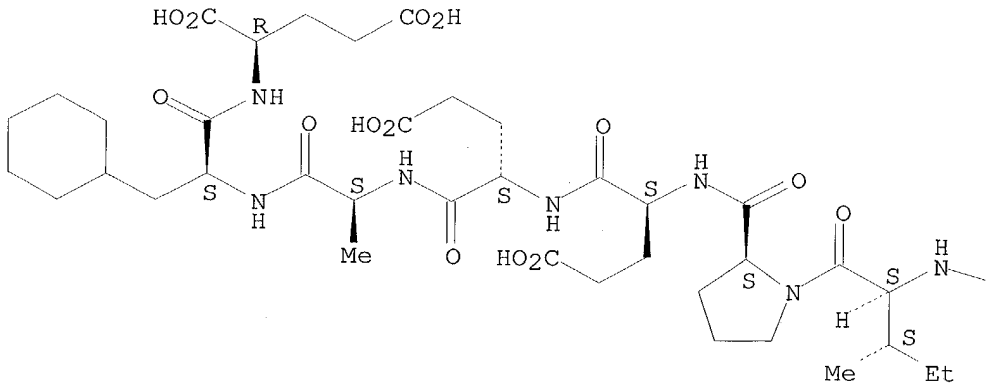
```
=> fil reg
FILE 'REGISTRY' ENTERED AT 18:32:38 ON 22 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   21 JUL 2003  HIGHEST RN 552272-14-7
DICTIONARY FILE UPDATES:  21 JUL 2003  HIGHEST RN 552272-14-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d l43 sqide can 1 10 20 30 40 50 60 70 80

L43  ANSWER 1 OF 81  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   263367-74-4  REGISTRY
CN   D-Glutamic acid, N2-[[4-(1,1-dimethylethyl)phenyl]sulfonyl]-L-arginyl-(2R)-
     2-piperidinecarbonylglycylglycyl-(2S)-2-cyclohexylglycylglycyl-.beta.-
     alanyl-L-.alpha.-aspartyl-L-tyrosyl-L-.alpha.-glutamyl-L-prolyl-L-
     isoleucyl-L-prolyl-L-.alpha.-glutamyl-L-.alpha.-glutamyl-L-alanyl-3-
     cyclohexyl-L-alanyl- (9CI)  (CA INDEX NAME)
FS   PROTEIN SEQUENCE; STEREOSEARCH
SQL  18
NTE  modified (modifications unspecified)
```

type	------ location ------		description
uncommon	Pip-2	-	-
uncommon	Aaa-5	-	-
uncommon	Bal-7	-	-
modification	Arg-1	-	undetermined modification
modification	Ala-17	-	cyclohexyl<Chx>

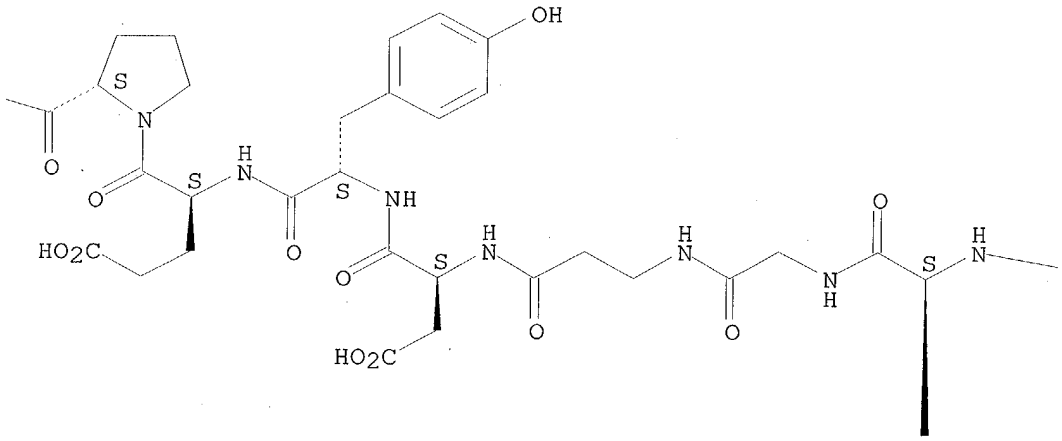
```
SEQ      1 RXGGXGXDYE PIPEEAAE
             =====
HITS AT:   3-7

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF   C100 H149 N21 O32 S
SR   CA
LC   STN Files:   CA, CAPLUS

Absolute stereochemistry.
```

Samples (I cannot display all of them - too expensive)

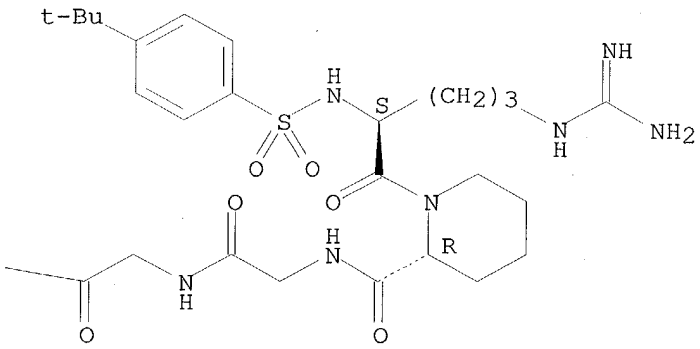
PAGE 1-A



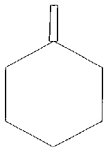
PAGE 1-B



PAGE 1-C



PAGE 2-B



1 REFERENCES IN FILE CA (1947 TO DATE)
1 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 132:262009

L43 ANSWER 10 OF 81 REGISTRY COPYRIGHT 2003 ACS on STN
RN **223122-27-8** REGISTRY
CN D-Glutamic acid, N2-[[4-(1,1-dimethylethyl)phenyl]sulfonyl]-L-arginyl-(2R)-2-piperidinecarbonylglycylglycyl-(.alpha.S)-.alpha.-aminobenzenebutanoylglycyl-.beta.-alanyl-L-.alpha.-aspartyl-L-tyrosyl-L-.alpha.-glutamyl-L-prolyl-L-isoleucyl-L-prolyl-L-.alpha.-glutamyl-L-.alpha.-glutamyl-L-alanyl-3-cyclohexyl-L-alanyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 18
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Pip-2	-	-
uncommon	Abu-5	-	-
uncommon	Bal-7	-	-
modification	Arg-1	-	undetermined modification
modification	Abu-5	-	phenyl<Ph>
modification	Ala-17	-	cyclohexyl<Chx>

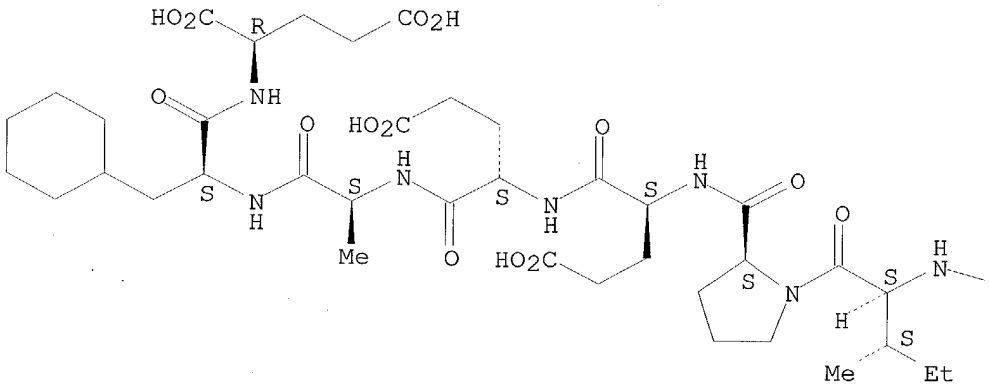
SEQ 1 RXGGXGXDYE PIPEEAAE
=====

HITS AT: 3-7

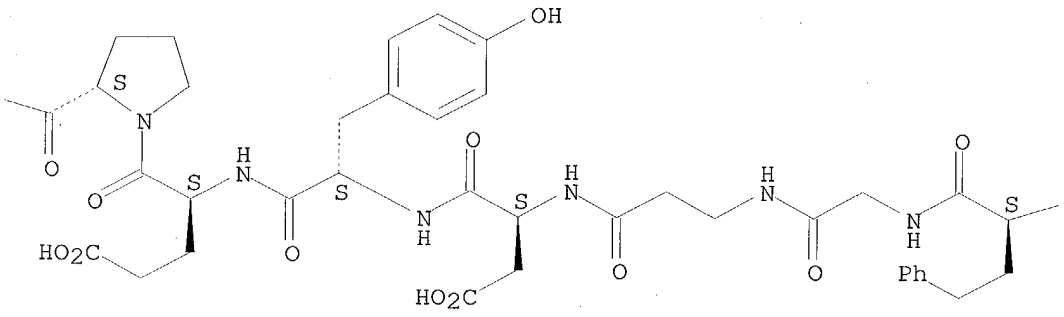
RELATED SEQUENCES AVAILABLE WITH SEQLINK
MF C102 H147 N21 O32 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

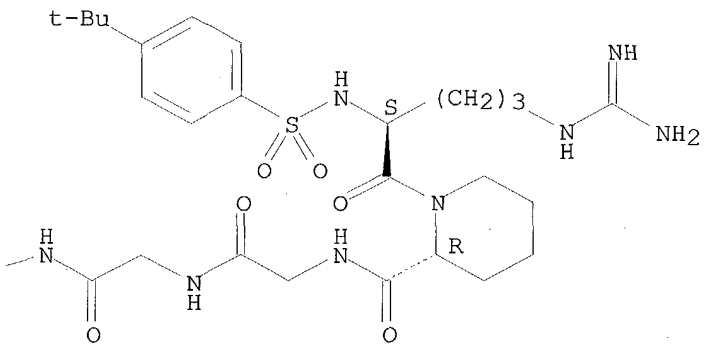
PAGE 1-A



PAGE 1-B



PAGE 1-C



2 REFERENCES IN FILE CA (1947 TO DATE)
2 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 132:262009

REFERENCE 2: 130:297001

L43 ANSWER 20 OF 81 REGISTRY COPYRIGHT 2003 ACS on STN
RN **223121-63-9** REGISTRY
CN D-Glutamic acid, N2-[[4-(1,1-dimethylethyl)phenyl]sulfonyl]-L-arginyl-(2R)-2-piperidinecarbonylglycylglycyl-D-isoleucylglycyl-.beta.-alanyl-L-.alpha.-aspartyl-L-tyrosyl-L-.alpha.-glutamyl-L-prolyl-L-isoleucyl-L-prolyl-L-.alpha.-glutamyl-L-.alpha.-glutamyl-L-alanyl-3-cyclohexyl-L-alanyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 18
NTE modified (modifications unspecified)

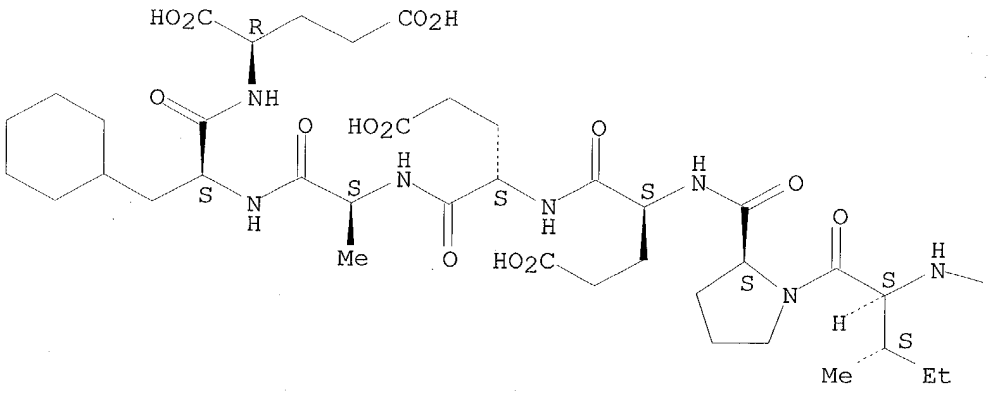
type	------ location ------		description
uncommon	Pip-2	-	-
uncommon	Bal-7	-	-
modification	Arg-1	-	undetermined modification
modification	Ala-17	-	cyclohexyl<Chx>

SEQ 1 RXGGIGXDYE PIPEEAAE
=====
HITS AT: 3-7

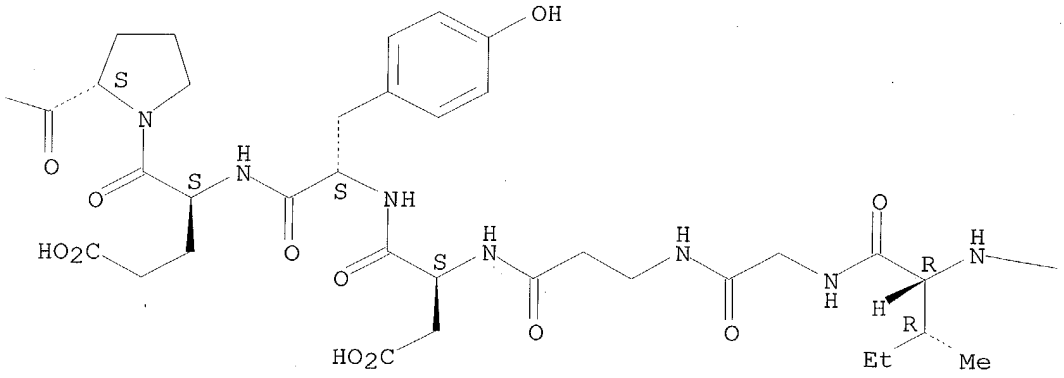
RELATED SEQUENCES AVAILABLE WITH SEQLINK
MF C98 H147 N21 O32 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

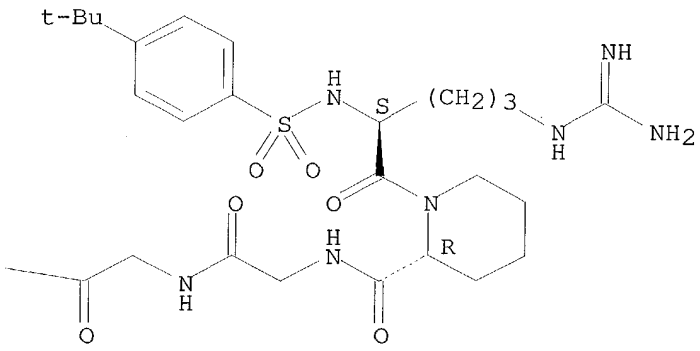
PAGE 1-A



PAGE 1-B



PAGE 1-C



2 REFERENCES IN FILE CA (1947 TO DATE)
2 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 132:262009

REFERENCE 2: 130:297001

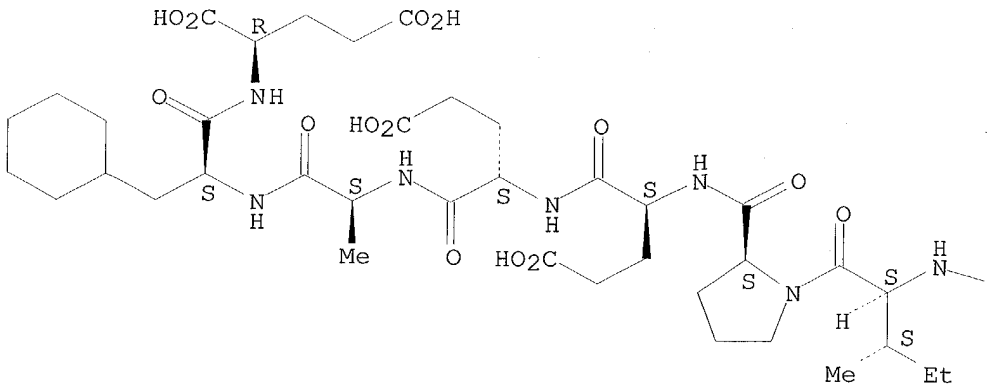
L43 ANSWER 30 OF 81 REGISTRY COPYRIGHT 2003 ACS on STN
RN **223121-04-8** REGISTRY
CN D-Glutamic acid, N2-[[4-(1,1-dimethylethyl)phenyl]sulfonyl]-L-arginyl-(2R)-2-piperidinecarbonylglycylglycyl-L-cysteinylglycyl-.beta.-alanyl-L-.alpha.-aspartyl-L-tyrosyl-L-.alpha.-glutamyl-L-prolyl-L-isoleucyl-L-prolyl-L-.alpha.-glutamyl-L-.alpha.-glutamyl-L-alanyl-3-cyclohexyl-L-alanyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 18
NTE modified

type	------ location ------		description
uncommon	Pip-2	-	-
uncommon	Bal-7	-	-
modification	Arg-1	-	undetermined modification
modification	Ala-17	-	cyclohexyl<Chx>

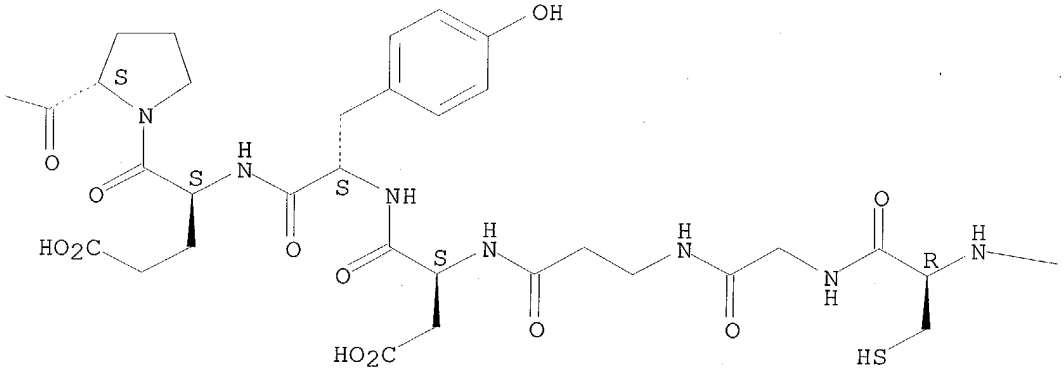
SEQ 1 RXGGCGXDYE PIPEEAAE
=====
HITS AT: 3-7
MF C95 H141 N21 O32 S2
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

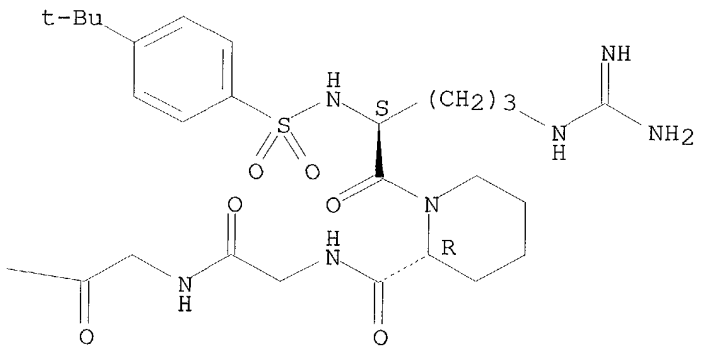
PAGE 1-A



PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1947 TO DATE)
1 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 130:297001

L43 ANSWER 40 OF 81 REGISTRY COPYRIGHT 2003 ACS on STN
RN **223119-87-7** REGISTRY
CN D-Glutamic acid, N2-[[4-(1,1-dimethylethyl)phenyl]sulfonyl]-L-arginyl-(2R)-2-piperidinecarbonyl-D-histidylglycylglycylglycyl-.beta.-alanyl-L-.alpha.-aspartyl-L-tyrosyl-L-.alpha.-glutamyl-L-prolyl-L-isoleucyl-L-prolyl-L-.alpha.-glutamyl-L-.alpha.-glutamyl-L-alanyl-3-cyclohexyl-L-alanyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 18
NTE modified (modifications unspecified)

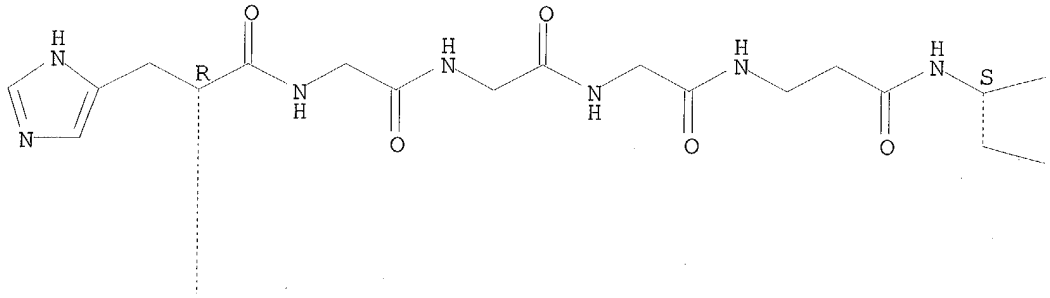
type	------ location ------		description
uncommon	Pip-2	-	-
uncommon	Bal-7	-	-
modification	Arg-1	-	undetermined modification
modification	Ala-17	-	cyclohexyl<Chx>

SEQ 1 RXHGGGXDYE PIPEEAAE
=====
HITS AT: 3-7

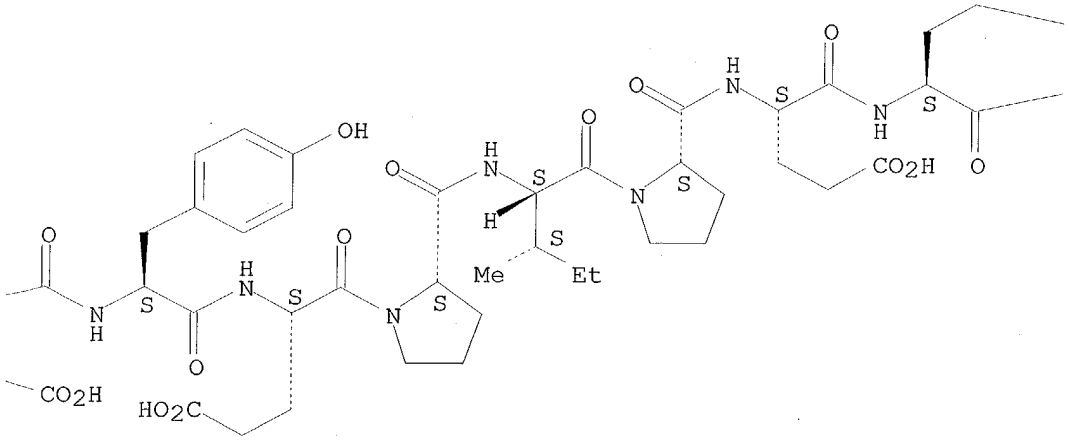
RELATED SEQUENCES AVAILABLE WITH SEQLINK
MF C98 H143 N23 O32 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

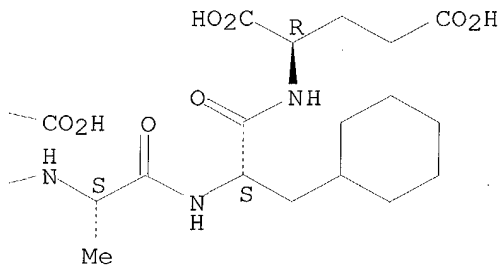
PAGE 1-A



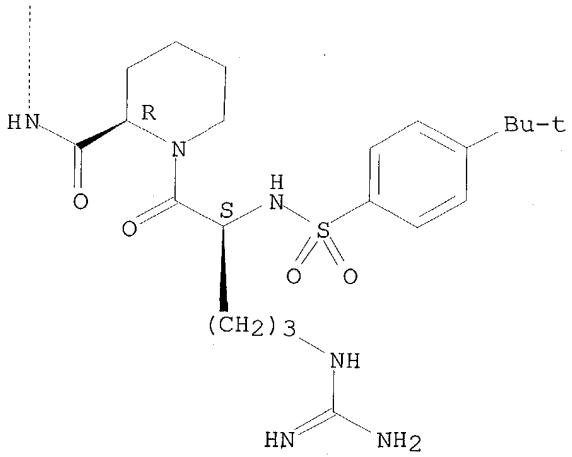
PAGE 1-B



PAGE 1-C



PAGE 2-A



2 REFERENCES IN FILE CA (1947 TO DATE)
2 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 132:262009

REFERENCE 2: 130:297001

L43 ANSWER 50 OF 81 REGISTRY COPYRIGHT 2003 ACS on STN
RN **223119-07-1** REGISTRY
CN D-Glutamic acid, N2-[[4-(1,1-dimethylethyl)phenyl]sulfonyl]-L-arginyl-(2R)-2-piperidinecarbonyl-2-cyclohexylglycylglycylglycylglycyl-.beta.-alanyl-L-.alpha.-aspartyl-L-tyrosyl-L-.alpha.-glutamyl-L-prolyl-L-isoleucyl-L-prolyl-L-.alpha.-glutamyl-L-.alpha.-glutamyl-L-alanyl-3-cyclohexyl-L-alanyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 18
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Pip-2	-	-
uncommon	Aaa-3	-	-
uncommon	Bal-7	-	-
modification	Arg-1	-	undetermined modification
modification	Ala-17	-	cyclohexyl<Chx>

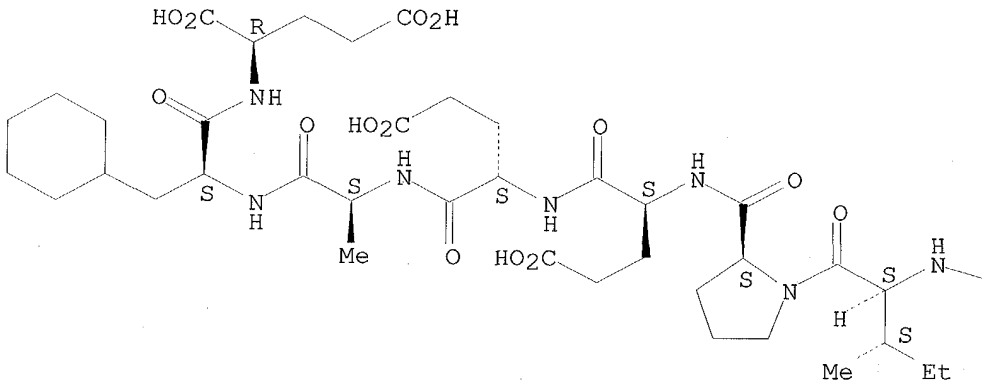
SEQ 1 RXXGGGXDYE PIPEEAAE
=====

HITS AT: 3-7

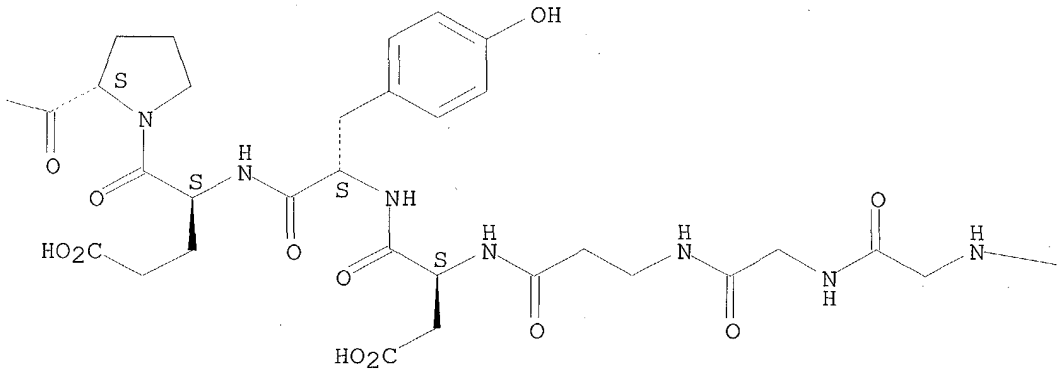
RELATED SEQUENCES AVAILABLE WITH SEQLINK
MF C100 H149 N21 O32 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

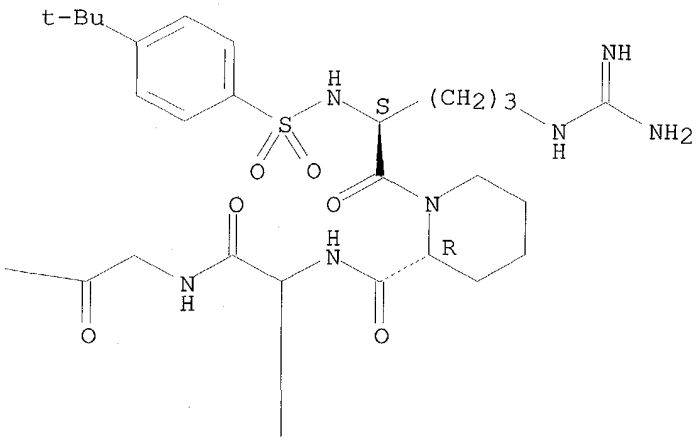
PAGE 1-A



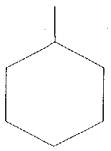
PAGE 1-B



PAGE 1-C



PAGE 2-C



1 REFERENCES IN FILE CA (1947 TO DATE)
1 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 130:297001

L43 ANSWER 60 OF 81 REGISTRY COPYRIGHT 2003 ACS on STN
RN **223118-31-8** REGISTRY
CN D-Glutamic acid, N2-[[4-(1,1-dimethylethyl)phenyl]sulfonyl]-L-arginyl-(2R)-2-piperidinecarbonyl-L-methionylglycylglycylglycyl-.beta.-alanyl-L-.alpha.-aspartyl-L-tyrosyl-L-.alpha.-glutamyl-L-prolyl-L-isoleucyl-L-prolyl-L-.alpha.-glutamyl-L-.alpha.-glutamyl-L-alanyl-3-cyclohexyl-L-alanyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 18
NTE modified (modifications unspecified)

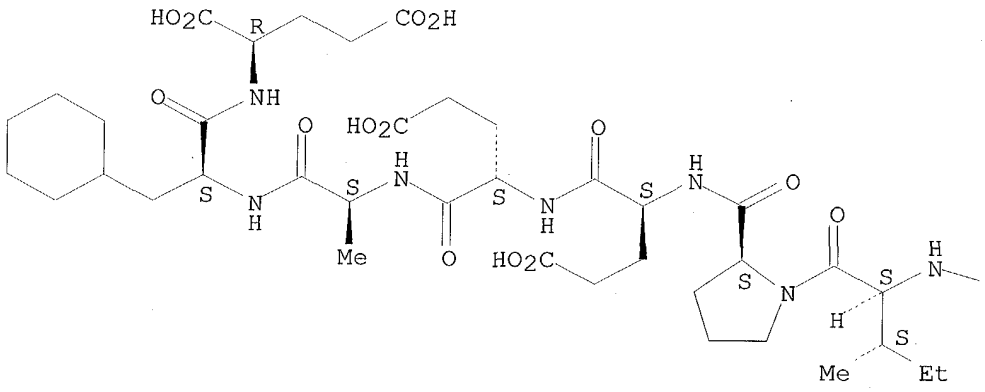
type	------ location ------		description
uncommon	Pip-2	-	-
uncommon	Bal-7	-	-
modification	Arg-1	-	undetermined modification
modification	Ala-17	-	cyclohexyl<Chx>

SEQ 1 RXMGGGXDYE PIPEEAAE
=====
HITS AT: 3-7

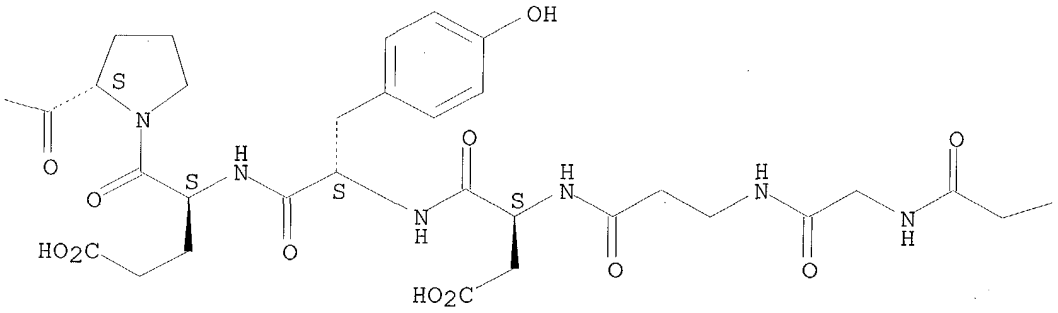
RELATED SEQUENCES AVAILABLE WITH SEQLINK
MF C97 H145 N21 O32 S2
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

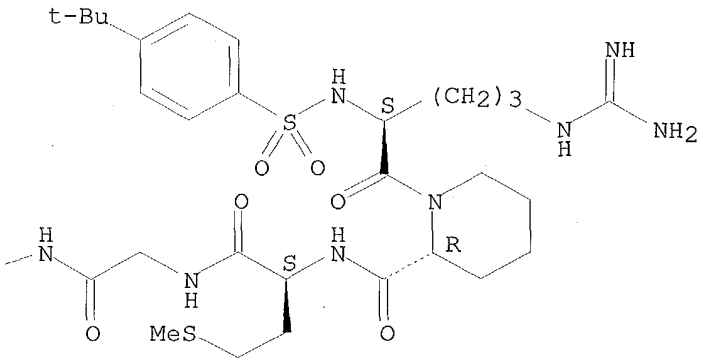
PAGE 1-A



PAGE 1-B



PAGE 1-C



2 REFERENCES IN FILE CA (1947 TO DATE)
2 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 132:262009

REFERENCE 2: 130:297001

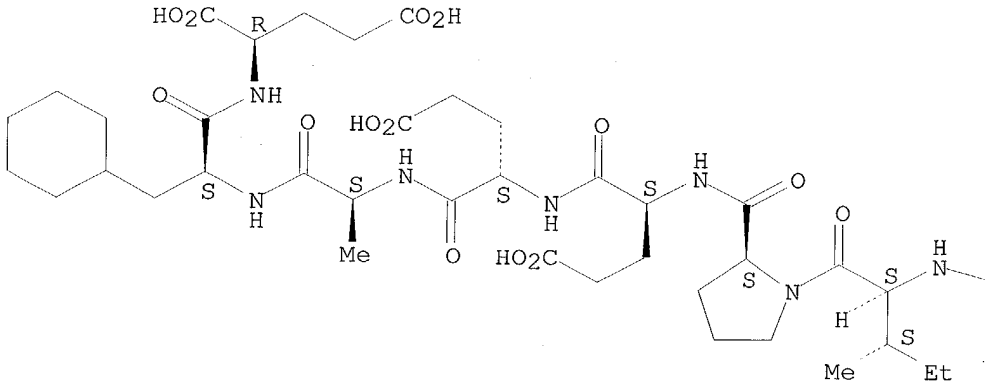
L43 ANSWER 70 OF 81 REGISTRY COPYRIGHT 2003 ACS on STN
RN **223117-53-1** REGISTRY
CN D-Glutamic acid, N2-[[4-(1,1-dimethylethyl)phenyl]sulfonyl]-L-arginyl-(2R)-2-piperidinecarbonyl-2-methylalanylglycylglycylglycyl-.beta.-alanyl-L-.alpha.-aspartyl-L-tyrosyl-L-.alpha.-glutamyl-L-prolyl-L-isoleucyl-L-prolyl-L-.alpha.-glutamyl-L-.alpha.-glutamyl-L-alanyl-3-cyclohexyl-L-alanyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 18
NTE modified

type	------ location ------		description
uncommon	Pip-2	-	-
uncommon	Aib-3	-	-
uncommon	Bal-7	-	-
modification	Arg-1	-	undetermined modification
modification	Ala-17	-	cyclohexyl<Chx>

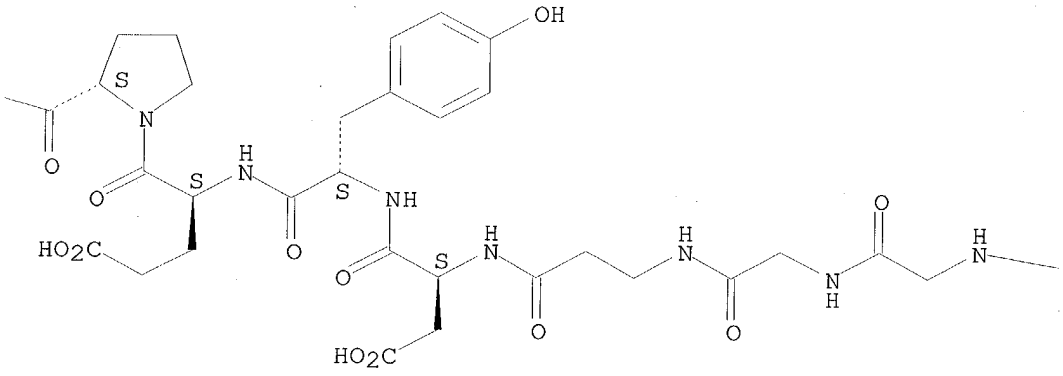
SEQ 1 RXXGGGXDYE PIPEEAAE
=====
HITS AT: 3-7
MF C96 H143 N21 O32 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

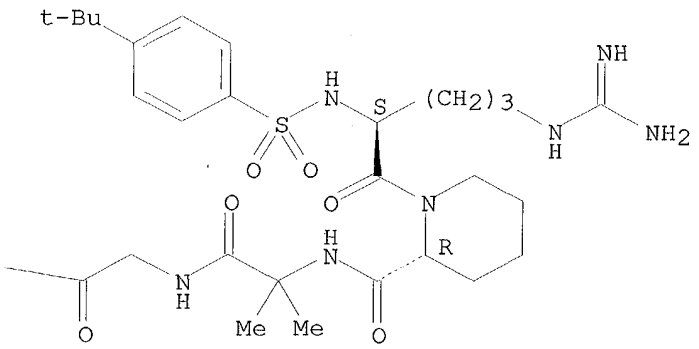
PAGE 1-A



PAGE 1-B



PAGE 1-C



2 REFERENCES IN FILE CA (1947 TO DATE)
2 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 132:262009

REFERENCE 2: 130:297001

L43 ANSWER 80 OF 81 REGISTRY COPYRIGHT 2003 ACS on STN
RN **197518-05-1** REGISTRY
CN D-Glutamic acid, N2-[[4-(1,1-dimethylethyl)phenyl]sulfonyl]-L-arginyl-(2R)-2-piperidinecarbonylglycylglycylglycylglycyl-.beta.-alanyl-L-.alpha.-aspartyl-L-tyrosyl-L-.alpha.-glutamyl-L-prolyl-L-isoleucyl-L-prolyl-L-.alpha.-glutamyl-L-.alpha.-glutamyl-L-alanyl-3-cyclohexyl-L-alanyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 18
NTE modified (modifications unspecified)

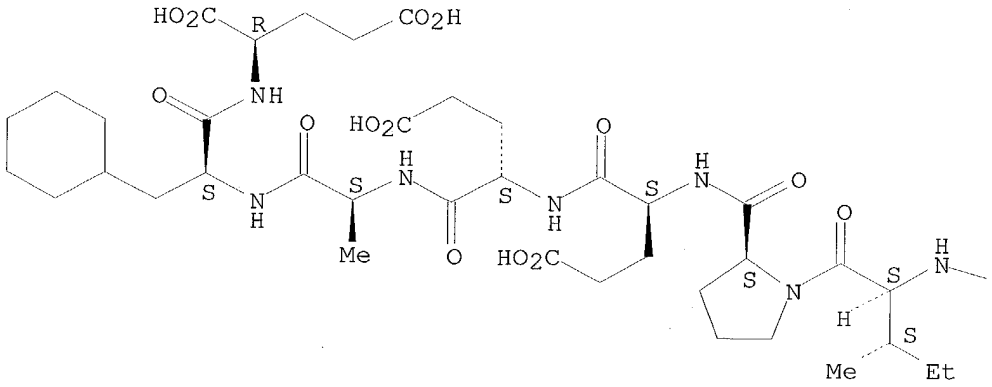
type	------ location ------		description
uncommon	Pip-2	-	-
uncommon	Bal-7	-	-
modification	Arg-1	-	undetermined modification
modification	Ala-17	-	cyclohexyl<Chx>

SEQ 1 RXGGGGXDYE PIPEEAAE
=====
HITS AT: 3-7

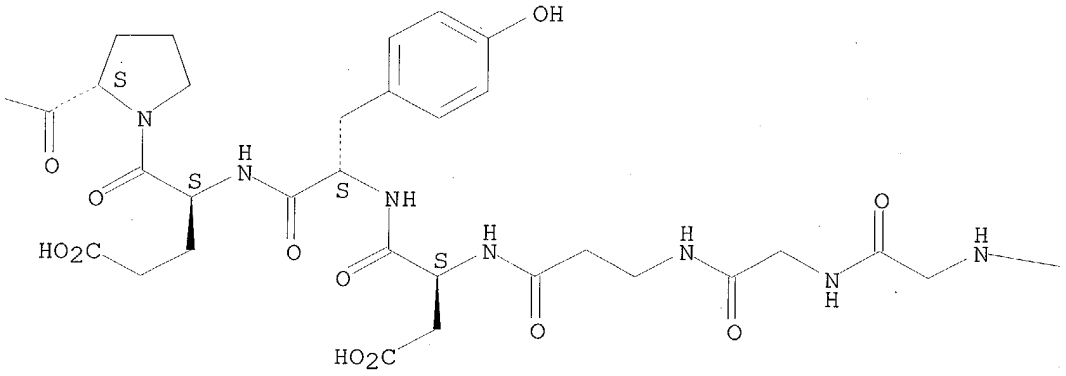
RELATED SEQUENCES AVAILABLE WITH SEQLINK
MF C94 H139 N21 O32 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

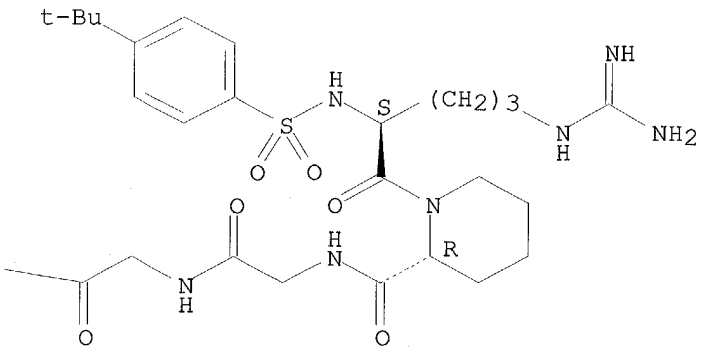
PAGE 1-A



PAGE 1-B



PAGE 1-C



3 REFERENCES IN FILE CA (1947 TO DATE)
3 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 132:262009

REFERENCE 2: 130:297001

REFERENCE 3: 127:316126